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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,414	08/31/2004	Gene Hung	HOUSEEI.006NP	8360

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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/506,414	HUNG ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

1. This application has been re-assigned to a new Examiner in a different Art Unit. Therefore, future correspondence should reflect such changes. Applicant is referred to the end of the Action for the appropriate contact information.

2. Applicant's response to a restriction requirement on May 11, 2006, is acknowledged. Applicant has elected the invention of Group I, Claims 1-14, with traverse, and the following restricted species: (a) human papilloma virus recited in Claim 2, (b) human papilloma virus type 16, as recited in Claims 4 and 11, and (c) a human papilloma virus, type 16, E6 and E7 genes, as recited in Claim 10.

   The Applicant's argument that the Invention I composition of a substantially pure cell line of non-tumorigenic, immortalized human Schwann or Schwannoma cells and a method of making said cell lines contributes over the prior art is persuasive.

   37 CFR 1.47(d) states: "If multiple products, processes of manufacture, or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT article 17(3)(a) and 1.476(c)." Thus, Claims 15-21, as the first method of using the substantially pure cell line of non-tumorigenic, immortalized human Schwann or Schwannoma cells, are rejoined to Claims 1-14.

3. Claims 22-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1-21 are under consideration.

Priority

5. Applicant's claim for the benefit of the prior-filed U.S. Provisional Application 60/361,528, filed March 1, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Specification

6. The disclosure is objected to because of the following informalities: the reference to Hung, G. et al, 1999, Int. J. *Oncogene* 14:409-15 (page 2, line 24, emphasis added) is in error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. **Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Nature of the Invention and the Breadth of the Claims

The inventive concept in the instant application is a substantially pure, immortalized, non-tumorigenic, human Schwann or Schwannoma cell line which express the HPV E6 and E7 genes. When the claims are analyzed in light of the specification, the instant invention encompasses an expansive genus of genetically and phenotypically diverse human Schwann and Schwannoma cell lines immortalized by one of many known immortalizing genes and oncogenes. Thus, the scope of the claims includes numerous structural and genotypically diverse variants, and the genus is highly variable because a significant number of structural differences between genus members is permitted.

The State of the Prior Art and the Level of Predictability in the Art

The art recognizes that many genes may be used to immortalize vertebrate cells. For example, Katakura et al (Method in Cell Biology 57: 69-91, 1998) teach a class of genes, including the SV40 T antigen, HPV type 16 E6 and E7, and adenovirus E1A, that are useful to immortalize primary cells of diverse cell types that are not abundant, difficult to obtain in pure form or have brief lifetimes in culture (pages 70-73), e.g. human Schwann cells. Similarly, Schlegal (U.S. Patent No. 5376542, December 27, 1994) teach a method for immortalizing any cell type using HPV-16, 18, 31, 33 or 35 E6 and E7 genes, wherein the immortalized cells retain the differentiated phenotypic characteristics of the parent cells (column 3, lines 1-4; columns 3-4, joining paragraph; column 6, lines 67-68; column 7, line 20). The art also recognizes that HPV E6 is a multi-functional protein that can inactivate the p53 tumor suppressor protein, which functions as a "guardian of the genome" by integrating various signal transduction pathways that sense cellular stress, and genotoxic and cytotoxic insults, and causes cellular growth arrest or apoptosis (Munger et al, page 215, column 2, lines 30-42). Inactivation of p53 by HPV E6 proteins thus allows the propagation of cells that have suffered genetic alterations, and as such contributes to genomic instability (Munger et al, page 217, column 1, lines 20-25). Similarly, the multi-functional HPV E7 protein inactivates a number of critical cellular regulatory proteins, including the retinoblastoma tumor suppressor protein pRB (Munger et al, page 219, column 2, lines 1-5). Because pRB negatively regulates the E2F transcription factor, whose targets include many proteins that encode enzymes that are rate-limiting for entry into S-phase, the binding of HPV E7 to pRB induces DNA synthesis and cellular proliferation. Furthermore, HPV E7 has been shown to induce abnormal centrosome duplication, resulting in multipolar, abnormal mitoses and anueploidy (Munger et al, page 221, column 2, lines 30-35). Thus HPV E7 synergizes with E6 to provoke genomic instability.

However, making an immortalized human Schwann cell line that is non-tumorigenic is not a routine practice. The art teaches that, even if human cells can be immortalized by several methods, it has been quite difficult to establish human cells that maintain functionality after immortalization, and that the immortalized cell lines are never normal, but represent transformed variants with some degree of tumorigenic potential (Katakura et al, page 79, lines 1-4). Although the transformation of a non-tumorigenic, immortalized cell into a tumorigenic immortalized cell

requires additional genetic lesions, the degree of genomic instability aggravated by HPV E6 and E7 protein activity during, and after, the immortalization process provides ample opportunity for such additional lesions to arise.

The Amount of Direction Provided by the Inventor and The Existence of Working Examples

The specification does not teach several important considerations to enable an artisan to make an immortalized human Schwann or Schwannoma cell line that is non-tumorigenic. The specification does not place a limit on the number of nucleic acid mutations and chromosomal duplications, deletions, translocations, etc... that may exist in a substantially pure, non-tumorigenic, immortalized human Schwann or Schwannoma cell line. The only other identifying characteristic recited for a non-tumorigenic, immortalized human Schwann or Schwannoma cell is that immortalized cells would have the property of maintaining the phenotypic characteristics of Schwann or Schwannoma cells. In the instant case, the specification describes the HEI-193 human Schwannoma cell line, deposited as ATCC #PTA-4544, derived from vestibular Schwannoma tissue (pages 13-14).

Furthermore, the HEI-193 human Schwannoma cell line that is deposited as ATCC #PTA-4544 (page 3, lines 8-10 and Figures 1-3 and 5-7) under the Budapest Treaty on July 11, 2002 with the American Type Culture Collection (ATCC) as ATCC #PTA-4544; however, a search of the ATCC catalogue was unable to identify these materials. Appropriate correction is required.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

However, the HEI-193 human Schwannoma cells are exceptionally abnormal, have diverse chromosomal complement, and manifest phenotypic traits that are not constant. The primary Schwannoma cells had already suffered genetic changes *in vivo* that transformed the cells from normal to neoplastic. Furthermore, once established *in vitro* and transfected with HPV E6 and E7 genes, the HEI-193 cells began to acquire additional, novel phenotypic properties

before and after the respective M1 senescence and M2 immortalization crises, such as increasing morphological heterogeneity, changes in cell proliferation rates, variation in S100 marker expression, and genomic instability such as changes in chromosome number and type (pages 13-15).

Katakura et al teaches that because immortalized human cells are never normal, they may express a tumorigenic phenotype to a varying degree (page 84, lines 1-3). Thus, given the genomic instability observed in these cells, an artisan can reasonably conclude that continuous proliferation of the HEI-193 cells will accumulate further genetic alterations, which may eventually transform these cells to be completely tumorigenic (page 16, lines 17-18).

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that an immortalized human Schwann or Schwannoma cell line other than the cell PTA-4544 is non-tumorigenic.

8. **Claims 1, 12-14 and 17 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "phenotypic properties" and "phenotypic characteristics" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "phenotypic properties" or "phenotypic characteristics"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d). "Phenotypic properties" and "phenotypic characteristics" are not defined in the specification and are generic to a universe of possibilities that are directly dependent upon the chosen means of measurement. For example, the method steps to molecularly assay a nucleotide sequence of the genome are distinctly different in design and mode of operation than the steps to molecularly assay mRNA expression, protein expression, rates of cell division, cell morphological features when cultured under various conditions, biochemical responses to diverse stimulants, etc... Each assay provides a distinct set of information that may correlate with, but is neither identical, nor equivalent, to the data yielded from another assay.

The specification teaches that the phenotypic traits of HEI-193 human Schwannoma cells are not constant. Claims 1 and 12 are drawn to immortalized cells that retain and maintain the phenotypic characteristics of the primary cells. The specification teaches that a retrovirus construct encoding the HPV E6 and E7 genes was transduced into primary human male vestibular Schwannoma cells at the second passage of the cells without drug selection (page 11, lines 11-21). Upon continued passaging, the HEI-193 cells began to acquire novel phenotypic properties before M1 senescence and after M2 crisis, as recited in Claim 12, such as increasing morphological heterogeneity, changes in cell proliferation rates, variation in S100 marker expression, and genomic instability such as changes in chromosome number and type (pages 13-15). Furthermore, given the genomic instability observed in these cells, continuous proliferation may accumulate further genetic alterations, which may eventually transform the HEI-193 cells to be completely tumorigenic (page 16, lines 17-18). Thus, the morphological, immunohistochemical, proliferative and karyotypic phenotypes presently described in the specification regarding the HEI-193 cells are merely descriptive "snapshots" of a heterogeneous population of continuously evolving cells.

9. **Claim 14 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is drawn to the immortalized human Schwann or Schwannoma cell recited in Claim 12, and further recites the limitation of a cell line having "the identifying characteristics" of ATCC #PTA-4544. The specification teaches that the HEI-193 cells, deposited as ATCC #PTA-4544, were established and designated upon recovery of drug resistant cells, recorded as Passage 0 (page 11, line 20). However, the specification does not disclose which passage number the HEI-193 cells deposited as ATCC #PTA-4544 had obtained. Numerous morphological, immunohistochemical, proliferative and karyotypic changes have occurred to the HEI-193 cells, documented at different passage numbers during propagation. Thus, the "the identifying characteristics" of the primary vestibular Schwannoma cells are distinctly different than the "the identifying characteristics" of the HEI-193 cells. Furthermore, the "the identifying characteristics" of the HEI-193 cells at each passage are distinctly different

from each other, as documented for Passages 6, 7, 9, 14, 17, and 40 (pages 3-4 and 11-16). Therefore, a cell line having the "identifying characteristics" of ATCC #PTA-4544 is indefinite.

, 2 clms dependent therefrom

10. No claim is allowed. Claims 13-14 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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